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08/469,492

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/469,492	06/06/95	WEINER H	1010/16959-U

18M1/0721

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EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1818	10

DATE MAILED: 07/21/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4/7/97.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 37-39, 42-49, 52-57 and 59-65 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 37-39, 42-49, 52-57 and 59-65 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Response to Amendment

1. The amendment filed April 7, 1997 has been entered into the record. Claims 37-39, 42-49, 52-57 and 59-65.

2. The Group and/or Art Unit of U.S. Patent application SN 08/469,492 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Group 1800, Art Unit 1818.

Information Disclosure Statements

3. The information disclosure statement filed, November 3, 1995, December 11, 1996 and January 15, 1997 have been considered with the following exceptions. The patent application references recited in the IDS filed November 3, 1995 have been lined through inasmuch as they are not prior art, in that US applications are not published documents and therefore not in the public domain. The examiner however appreciates applicants identification of parent and related applications present in the office. In the IDS filed November 3, 1995, the art citation numbers 10-70 have not been considered because no copy was available in 07/843,752 as indicated by applicants. These references will be considered when a copy is provided.

Rejections Withdrawn

4. The rejection of claims 37, 38, 40-45, 48, 49, 51-55 and 58 under 35 U.S.C. 103 as obvious over Foster in view of Davydov et al or Ecanow is withdrawn in view of applicants amendments.

5. The rejection of claims 37-39, 41-45 , 48, 49 and 51-55 as being obvious over US Patent 5,399,347 is withdrawn based on applicants amendment.

6. The provisional rejection of claims 37-39, 40, 42-45 , 48, 49 and 51-55 as being obvious over 08/419,502 is withdrawn based on applicants amendment.

7. The provisional rejection of claims 37-58 as being obvious over 08/328,562 is withdrawn based on applicants amendment.

8. The provisional rejection of claims 37-58 as being obvious over 08/427,016 is withdrawn based on applicants amendment.

Rejections Maintained

9. The rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 under 35 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 37-58 in Paper No. 6, mailed 12-31-96.

Applicant asserts that the one of skill in the art could obtain the GAD antigens and use them to treat Type I diabetes and provides a reference which teaches the cDNA of GAD and that methods of purification were known for rat and mouse. This is not persuasive because the claims are drawn to humans, one of skill in the art would not a priori administer a protein from another species due to the well established immunological problems of administration of therapeutic proteins from different species into humans. Moreover, the Tian et al reference merely supports the examiners position stating as late as 1996 on page 1562, column 1, that:

> "... evidence demonstrating the protective effects of Th2 cells in autoimmune disease has been largely confined to experimentally induced diseases."

One of skill in the art would have ample reason to question the enablement of the specification which relies upon a tight correlation of human and experimental animal responses. However, there are numerous instance in the art where reliance on an animal models have been shown not to correlate with the efficacy in humans. For example, the art teaches that while myelin basic protein showed very promising results in animal models, such results were not correlated in humans. The subsequent human studies demonstrated no significant differences between the test and control groups (BioWorld Today. Volume 8, Number 77, pages 1-4). While the EAE mouse showed promise, the clinical trials failed to demonstrate any reproducible benefit using the teachings of the EAE mouse as an experimental start point. It is clear from these trials in the art that mouse models do not *a priori* predictably and reproducibly correlate with an appropriate human response. Moreover, Tian et al also teach:

> "... it is unclear what modes of antigen administration would induce Th2 responses, whereas antigens are easily delivered to mucosal surfaces, this treatment has been recently reported to induce a variety of T cell responses (i.e. peripheral deletion, anergy, and activation of CD4+ and CD8+ cells, references 4, 6, 14-16). Here, we show in NOD mice, that a single nasal administration of GAD65 peptides, **before the onset of autoimmunity** [emphasis added] , induces a Th2 cell response that actively diverts/downregulates the development of autoreactive Th1 responses and inhibits autoimmune disease progression."

Only when the peptides are administered before the onset of autoimmunity is any affect observed. This is not the instant case, in humans wherein autoimmunity is in progress when treatment is begun and the GAD is administered **after** the onset of the disease. There is thus no evidence that administration of any specific bystander antigen when administered as instantly

claimed is therapeutically effective in humans. Moreover, specific T cell target determinants were administered in combination. There is no guidance in the specification for the selection of these particular peptides nor the route of administration (i.e. nasal), nor is their any indication in the specification that these are not autoantigens. The only written description support in the specification for the instantly claimed ".. wherein said bystander antigen is not an autoantigen in said human and wherein said bystander antigen is not an insulin antigen." is for glucagon on page 19, lines 15-23. The specification merely invites one of skill in the art to further experimentation. Thus, the arguments and evidence is not commensurate in scope with the claims at hand. The rejection is maintained.

10. The rejection of claims 48-49, 52-55, and new claims 56, 62, 63, and 64 under 35 U.S.C. 102(b) as being anticipated by the Merck Manual is maintained for reasons made of record for claims 48-50 and 52-55 in Paper No. 6, mailed 12-31-96.

Applicant assert that the indented use of the composition is for subcutaneous administration. This is not persuasive because the mode of administration does not impart a patentable distinction to composition of glucagon in a pharmaceutically acceptable diluent. Moreover, it is well known in the art that parenteral solutions can be used for topical, nasal and oral administration. The rejection is maintained.

11. The provisional rejection of claims 37-39, 42-49, 52-57 and 59-65 as previously applied to claims 37-58 as being obvious over 08/472,017 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

12. The provisional rejection of claims 37-45, 47-55, and 57 and new claims 59-65 as previously applied to claims 37-45, 47-55, and 57 as being obvious over 08/461,591 is

maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

13. The provisional rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 as previously applied to claims 37-58 as being obvious over 08/461,662 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

14. The provisional rejection of 37-39, 42-48, 52-57 and new claims 59-65 as previously applied to claims 37-46 and 48-58 as being obvious over 08/468,996 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

New Rejections Based on Amendment

Claim Objections

15. Claims 37, 39 and 65 are objected to because they are essential duplicates. Claims 37 and 39 are identical in scope. Although the language of claim 65 is not identical to either 37 or 39, the recitation "is not an antigen to which T-cells which mediate the disease are sensitized" is by definition an autoantigen and therefore does not differ in scope. Correction is required.

16. No claims are allowed. All claims stand rejected.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application should be directed may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, it is recommended that the current FAX number for Group 1800 be obtained from the Group receptionist whose telephone number is (703) 308-0196.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Patricia A. Duffy, Ph.D.
July 16, 1997

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800